Dockets Management Branch (HFA-305),
Food and Drug Administration,
5630 Fishers Lane, rm. 1061,
Rockville,
MD 20852

TIBOTEC

Tibotec Pharmaceuticals Ltd.
Blanchardstown Corporate Park
Blanchardstown, Dublin 15
Ireland
Tel. + 353 1 820 81 14
Fax + 353 1 820 80 82

Dublin, 8th December 2000

Dear Sir or Madam,

Re: Guidance for Industry, Botanical Drug Products – Comments
Docket No. 00D-1392, CDER 97113

On behalf of TIBOTEC, I wish to provide you with comments on the draft Guidance for Industry, Botanical Drug Products, of August 2000.

Introduction

TIBOTEC is an emerging, globally oriented pharmaceutical company, focused on discovering and developing superior pharmaceuticals for unmet medical needs. The scientific background of the company lies in the field of HIV infection and AIDS, infectious diseases (e.g. Leishmaniasis and tuberculosis), cancer and Alzheimer's disease.

TIBOTEC's headquarters and European R&D centre are located in Mechelen, Belgium. The US R&D laboratory, TIBOTEC, Inc., is located in Rockville, Maryland, USA. TIBOTEC's commercial activities are coordinated through TIBOTEC Pharmaceuticals Ltd., located in Dublin, Ireland. TIBOTEC Group NV was founded in 1994 by Rudi Pauwels, PhD, and Carine Claeys, pharmacist, with the objective of performing drug discovery and pre-clinical drug profiling in the focus areas. Paul Stoffels, MD, joined in 1997, when the target was extended to the establishment of an integrated pharmaceutical company. Dr. Pauwels authored the first paper describing the non-nucleoside HIV Reverse Transcriptase inhibitors (TIBO-compounds; *Nature 1990*).

TIBOTEC leverages intensive R&D efforts in AIDS drug discovery, resistance biology, and drug discovery technologies, such as ultra high-throughput screening, structure-based drug design and bio-informatics. The company has combined automation with intelligent image analysis methods to enable high-content screening of chemical libraries in cellular assays using a novel ultra high-throughput format. Drug discovery technologies, including structure-based drug design methods, are all aimed at increasing the speed and efficiency of target selection, assay design, and lead optimization.

Comments

In general, we are in agreement with the Guidance for Industry, Botanical Drug Products and we are pleased that such guidance is being drafted and will soon be available to industry.

00D-1392

I
C 24

Nevertheless, we would like to express our concerns regarding the terms 'highly purified' and 'botanical drug substance' as used throughout the document. In the annex to these comments is an example of a purified botanical drug substance, upon which our concerns are based. In our opinion, this mixture should be considered as a botanical.

From the guidance, however, it is unclear given the level of purification as outlined in the annex, whether this botanical substance or mixture of substances is indeed considered a 'botanical'. More specifically, it is not clear if the unspecific term '.... or other similar process.' (as used in the sentence beginning 'It is prepared.....' In the definition for a Botanical Drug Substance) would apply to purification techniques such as those outlined in the example.

We therefore would like to see further clarification of the terms 'highly purified' and 'botanical drug substance' as used in this document with regard to specific stages and methods/techniques of processing.

We hope that the Centre for Drug Evaluation and Research will find these comments useful and consequently we hope to see them reflected in the final Guidance for Industry, Botanical Drug Products document.

Please contact me should you require more information or clarification.

Yours sincerely,

Fiona McAndrew
Regulatory Affairs Officer

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Blanchardstown Corporate Park,
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Ireland.
tel + 353 1 8208114
fax + 353 1 8208082
email fiona.mcandrew@tibotec.com

ANNEX

PURIFIED BOTANICAL DRUG (SUBSTANCE)

1. INTRODUCTION

The composition of a botanical drug may vary from very complex and poorly defined (an extract) to a (partially) defined purified extract using different purification techniques.

The product referred to in the comment document is a purified botanical drug obtained by the process described in more detail below.

2. PROCESS

Basically the production process consists of 3 steps:

- solid-liquid extraction of plant leaves
- liquid-liquid extraction and washing (purification)
- additional purification

The result of this process is a (partially) defined botanical extract.

2.1. Extraction

Dried and milled plant leaves are extracted with ethanol 70° by repeated maceration overnight and percolation, at a ratio plant material:alcohol of 1:5.

2.2. Initial purification

The ethanolic botanical extract is concentrated and purified by consecutive liquid-liquid extractions. These extractions facilitate the removal of lipid constituents (water//hexane) and water-soluble components (water/butanol). The semi-purified botanical extract is obtained by precipitation in aceton and washing with other organic solvents.

2.3. Purification

The final purification is performed using one or more different purification techniques.

Tannins are removed on a gel (Sephadex).

Filtration on a reversed phase packing possibly removes more polar and/or more lipophylic fractions.

Depending on the technique(s) used, a purified extract with a different composition can be obtained. The purified extract contains at least 6 identified active compounds and a matrix consisting of related compounds (unidentified but structurally related compounds) and other unknown compounds (such as inorganic salts).

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1 From (Sender)

Account no. [redacted]

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Sender's reference *first twelve characters will be shown on invoice*

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[redacted]

[redacted]

[redacted]

Postcode

Phone / Fax / Telex: 353 1 8208114

2 To (Receiver)

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7630 Fishers Lane, Rm 1061
Rockville, MD 20852

Postcode: 20852 USA

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- [ ] External Billing Agreement
- [ ] Transport Collect

Shipment insurance *see reverse*

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Full description of contents

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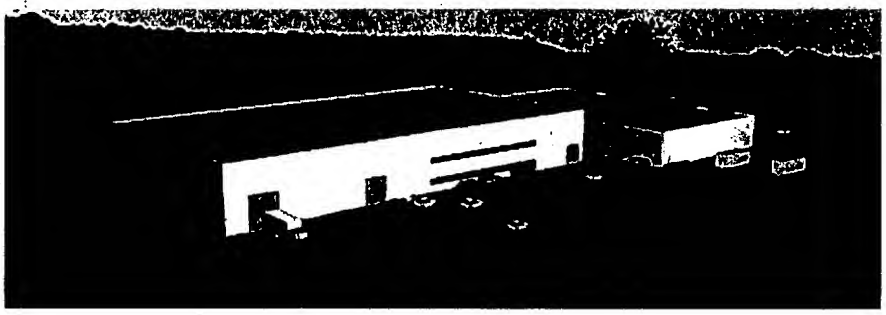
l'Ami des ingrédients naturels

April 2001 • Nr 27

Towards an ethics for development «natural»?

bringing substance pable of supporting the values of natural brands to the green label

We are pleased to announce the extension project of our manufacturing unit in Fontenay Sur Eure : Adonis. This new factory is dedicated to all of you, readers of l'AMI - who have made the choice of quality by Le Natural Product Designer*. This project is also a result of the still strong and growing vogue for natural products.



At the beginning of this new millennium, the panicking fear of the mad cow or genetically modified organisms even seem to add a further dimension to the «green wave». Is there only some agreement on the definition of the word natural?

Is the chamomile extract in this shampoo the same chamomile shown on the packaging of this soothing cream? They have the same INCI name.... The wave may well be just... a wave precisely: rising and rolling on... nothing.

Would this all be but wind ? No. At least this is the answer we have been trying to substantiate since the first issues of l'AMI - it may even be the vocation of this news letter.

Continued P3

These molecules we extract

These molecules we extract and we call «cosmetic actives» are mostly generated by the secondary metabolism of plants (the primary one involving respiration and photosynthesis). In particular, they allow the adaptation of plants to their environment.

Adaptation to the environment

To cold

Plants of temperate climates adapt themselves to cold. Frost provokes ice crystals in cells, which damage their membranes and kill them. The most visible defence system to avoid this phenomenon is the loss of leaves in winter. Moreover, an accumulation of «antigel» molecules takes place in some plants (amino-acids, carbohydrates and derivatives) to lower the freezing point of the plant.

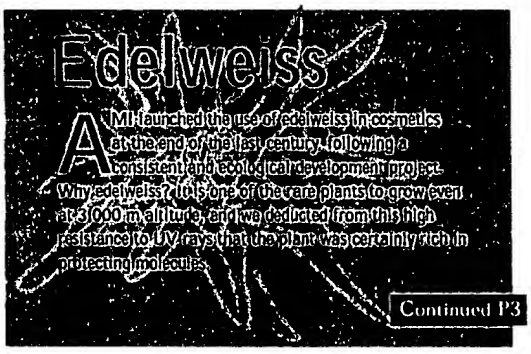
To aggression of parasites, predators, disease

Again, plants synthesize defensive and protective active molecules, mostly antibacterial and anti-fungal (particularly in essential oils) and even toxic to avoid consumption by animals.

To altitude

Further to the cold and dry conditions it generates, the mountain environment submits plants to another aggression: that of UV rays, the quantity of which increases by about 7 % each 300 m in altitude. This explains why plants rise in tiers on mountains. They become rarer and smaller with altitude. Besides these modifications visible to the bare eye, plants which resist to high altitude develop a protecting system of molecules able to screen out UV rays.

Continued P2



The large molecule families of the secondary metabolism

Terpenoids

They include phytohormones, numerous aromatic compounds particularly present in essential oils, the important carotenoid group, etc.

Alkaloids

They are often toxic molecules: curare, strychnine, cocaine. Caffeine is one of the rare alkaloids to be used in cosmetics (as a slimming active).

Phenolic compounds

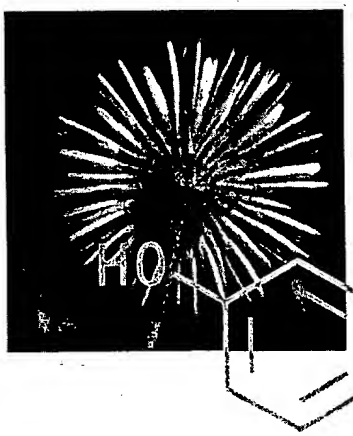
This is a large family with very interesting therapeutic and cosmetic properties. The structure of these substances can be defined as having at least one aromatic cycle and at least one hydroxyl function. Micro-organisms and plants only are able to synthesize the aromatic cycle, «building block» of phenolic compounds.

Let us review the main families and some examples of molecules:

- **Phenols:** skin whitening arbutin (in a number of plants of the Ericaceae family, particularly bearberry).
- **Phenolic acids:** salicylic acid and its derivatives (in willow bark and meadowsweet) which have anti-inflammatory properties: they are at the origin of aspirin.
- **Tannins:** which combine to proteic molecules. Due to this property, they allow to «waterproof» the upper layers of the epidermis and protect the layers underneath.
- **Coumarins**[1]: there are about a thousand of them. Let us quote umbelliferone, present in particular in mouse-ear, and its bacteriostatic properties.
- **Flavonoids:** more than 3 000, they have a common biosynthetic origin. They are pigments widely spread in plants. Flavonoids are mainly known for their free radical scavenging properties (notably against the peroxidation of cell membrane lipids).

Some of them belong to the «collective unconscious» of the cosmetic industry: hyperoside of St John's wort, PCO of grape seeds, anthocyanins of red vine, soybean isoflavones, sylimarin of blessed thistle or gingketin of ginkgo.

1. Coumarins come from the vernacular name of the tonka bean: coumarou, from which coumarin was isolated in 1820.



From the molecule to the formula : the new Frontier of natural

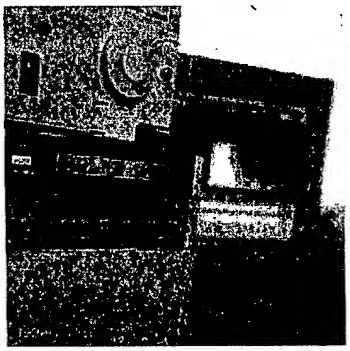
Many molecules reviewed hereabove are used as cosmetic active principles under the form of extracts at doses hardly ever exceeding 0.5 %.

It then is quite easy to understand that this concentration shall not be enough for a product to be qualified of natural. The proportion of «natural» can be substantially increased if working the base of the formula with plant derived formulation ingredients moreover displaying biological properties:

- vegetable oils which can go in the oily phase or emulsions while improving moisturization;
- proteins and lipids (lecithins), some of them being emulsifying, which protect and nourish the epidermis;
- thickening polysaccharides or gelling agents (carragheenans, gums...) which give products a nice texture while moisturizing the skin.

The natural base will thus be the next cosmetic territory to investigate. AMI signed for it, following the same philosophy as for plant extracts: rigour and objectivity.

Our laboratories are at your disposal to go even further. So give your skin a new start for the third millenary with cosmetics made of all natural and active ingredients!



increase the proportion of natural in cosmetic products by working the formula up

«natural»?

Natural ? Maybe should we start with a definition of the word or at least to review the semantic territory it covers.
An ingredient is said «natural» when derived from vegetable resources, with high care not to damage its nature.
It is the case for herbal extracts, provided the extraction process respects the nature of the extracted molecules.
Historical source of skin care materials, natural products, traditionally ill-defined, have been slowly overtaken by scientific synthetic chemicals.
But this is not enough to dismiss their potential: powerful analytical techniques as well as modern agriculture provide the conditions for a rational renewal of natural skin care based on the numerous biologically active molecules synthesized by the plants. Viewed from the angle of vegetable chemistry, natural products may indeed satisfy the expectations of scientists as well as those of consumers: the vegetable molecule bridges the gap between the world of plant and the formulation laboratory, between the marketing story and efficacy.

the vegetable molecule bridges the gap between the world of plant and the formulation laboratory, between the marketing story and efficacy

If the industry has long questioned its members on the subject of myth and reality, the vegetable molecule, the missing link of cosmetics, is finally bringing the best of both world together.

The molecule perspective allows a complete organization of the natural supply chain:

- in order to optimize the yield in active materials of the plant, terms and conditions are precisely defined with producers;
- extraction techniques are designed to obtain the molecule in a stable and usable form;
- analytical methods are defined to guarantee the presence and the concentration of the molecule in the product;
- extracts are standardized for reproducible evaluation tests.

a lot of brands have engaged on a road of quality

All these guarantees condition the value and legitimacy of natural products. And it is on this validated ground that the natural label may authorize brands to write claims actually in relation to facts. Because they... deserve it !
It is true that when naturals become so important, many laboratories have decided to buy the label at the lowest cost: an INCI name is bought at the cheapest price. But the continuous growth of the Alban Muller Group also testifies that a lot of brands have engaged on the road to quality - looking for precisely defined products with reliable guarantees on the origin and the manufacturing process.

to seize the full meaning of naturals

The Alban Muller Group now offers product development assistance service in 45 countries.
Experts help you determine the technical parameters of you project - their laboratories and manufacturing units become yours to develop products adapted to your needs - but also adapted to the ethics of your brands : to seize the full meaning of naturals.

Meetings

Vitafoods

APRIL 24-26 • GENEVA • AMI VARISTOR
Catherine Douay catherine_douay@compuserve.com
Fabienne Kirchenbaum fabienne.kirchenbaum@albanmuller.com
Isabelle Nault isabelle.nault@albanmuller.com
Jean-Marc Seigneuret jmseig@albanmuller.com
Varistor info@vari-food.ch
Expect your visit at Palexpo - Booth 1512
1218 Le Grand-Saconnex - Geneva - Switzerland

In-cosmetics

APRIL 24-26 • DÜSSELDORF • AMI WORLEE
Adeline Courtier adeline.courtier@albanmuller.com
Ariane Csendes ariane.csendes@albanmuller.com
Armelle Magré amagre@albanmuller.com
Alban Muller the_boss@albanmuller.com
Worlee Mschwoy@ch.worlee.de
Expect your visit at Messe-Center - Booth 260
Hall 3 - Düsseldorf - Germany

X Congreso Nacional de la Química Cosmética

MAY 17-20 • IXTAPA ZIHUATANEJO • AMI ABA
«Nature and science at the service of the cosmetic industry»
Alban Muller the_boss@albanmuller.com
Reinhard Richter aba_ventas2@infosel.net.mx
Expect your visit on Alban Muller's lecture
at Melia Azul Ixtapa Resort & Conference Center
Ixtapa Zihuatanejo - Mexico

SFC

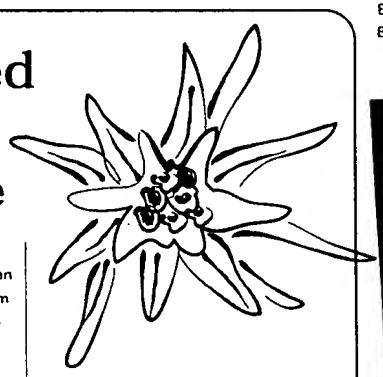
JUNE 6-7 • PARIS
Alban Muller International expects your visit on the occasion of the 50th anniversary of the SFC at Palais des Congrès de Paris - Level 2 - Hall Maillot A
Contact Sophie Lemoine sophie.lemoine@albanmuller.com

HBA

JULY 24-26 • SAO PAULO • AMI PIC
Alban Muller the_boss@albanmuller.com
The team **PIC QUIMICA** import@pic-quimica.com.br
Expect your visit at Expo Center Norte
Booth 150 - Sao Paulo - Brazil

Reasonable and integrated use of nature

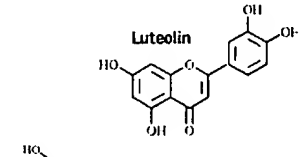
Edelweiss : a successful example

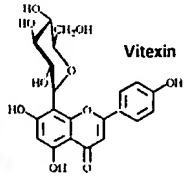


Adaptation to altitude by an increased synthesis of polyphenols

True mascot of the Alpine region and symbol of purity, edelweiss is a small annual plant with a fleecy aspect. What seems to be flowers are in fact the leaves disposed in a star shape and with a more fleecy aspect than the rest of the plant. The actual flowers are very small and not very decorative.
Edelweiss geographical origin is the Siberian steppes, where it resists to deep cold thanks to its downy and insulating coating made of thin hollow hairs.
Edelweiss grows mostly in rocky and sunny high mountain pastures, or calcareous rocks at an altitude of 800 to 3 000 m. It blossoms from June to September. It can grow in the snow, which gives it its image of purity and whiteness.
To be able to cope with such harsh climatic conditions, the plant must have adapted itself by a natural protective system not only against the cold, but also against U.V. rays which are particularly abundant at high altitudes. This physiological defence system consists in an efficient array of molecules resulting from the secondary metabolism with screening and antioxidant properties. The following molecules were put in evidence :

- flavonoids, particularly luteolin and apigenin and their glucosides : luteolin-7-glucoside and apigenin-7-glucoside, vitexin-2-rhamnoside ;
- phenolic acid of the cafeyl quinic type.





From an ecological point of view

Collecting edelweiss is submitted to regulations. We therefore set up a contract of integrated farming culture, within a programme of restoration of the Alpine sites.

Edelweiss: a cosmetic dream

From the German words edel, noble, and weiss, white, «edelweiss» itself evokes snowy summits, purity, original nature. In other words, it is an invitation to breathe the purest atmosphere thanks to extracts rich in protective molecules.
AMI offers in standard a watersoluble extract (propylene glycol) and an extract titrated in flavonoids (water and propylene glycol).

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E-mail : info@albanmuller.com
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Société Anonyme au capital de 40 000 €
RCS de Créteil numéro B 415 392 422
Président : Alban MULLER - Directeur Général : Laurent MULLER

L'AMI des Ingrédients Naturels

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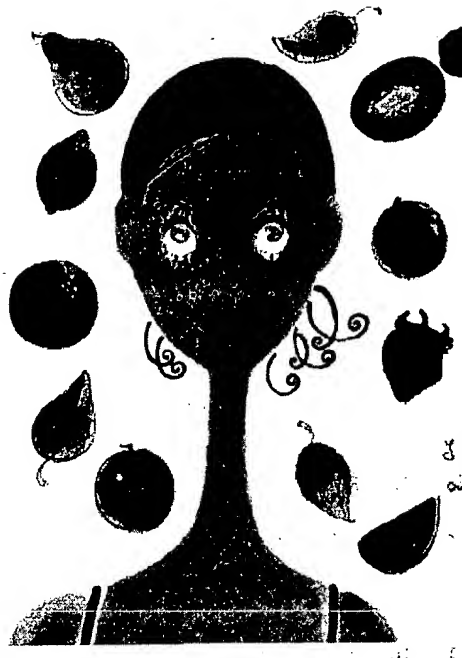
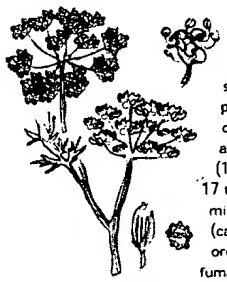


Regeneration : *millenium green*

According to the prophets, God created three realms that fill the three heavens. The first sphere, the love sphere, is red, the second sphere or sphere of wisdom is blue, the third sphere, sphere of creation, is green. Expressing soul regeneration, green also conveys the fecund union between water and earth. It stands for natural rebirth at ngtime, for renewal. It is the colour of youth, the colour of promises of a good arvest. Highly refreshing, green means sap, vegetable blood, life bud. Green also stands for harmony and serenity. It soothes emotions, eases a tense atmosphere, stimulates respiration and is an invitation to inner peace. It is a damp and lively colour, the colour of calm. Now then, why not come ind concoct new products? Come and have a rest for a cosmetic picking of ens. To feel fresh as running water, frisky as young herbs, sparkling as young shoots. To get a good dose of energy and colour your cosmetics with sharp hints. AMI presents its Spring regenerating selection of titrated extracts : watercress, fennel and cucumber with tonic, free-radical scavenging and moisturizing virtues.

I think beauty is a question of balance, I expect products to maintain and supplement the delicate mechanism of my skin

Free-radical scavenging fennel



Foeniculum vulgare Mill.

Fennel has soothing, antiseptic, scrubbing, purifying and free radical scavenging properties. Fennel extracts can be used in body care products (scrubbing creams and gels), soothing care for the eye contour, face products for tired, sensitive and mature skin and also in hand products. The seed contains glucids (oses and osides), protids (16 to 20 % proteins), 17 to 20 % lipids, mineral matters (calcium, potassium), organic acids (citric, fumaric, malic, tartaric, ascorbic), phenolic compounds (phenolic acids -caffeic, ferulic, paracoumaric), flavonoids of the flavonol type (quercetine and kaempferol derivatives), coumarins, terpenoids (triterpenes and carotenoids), vitamins (B1, B2, B3, B5, B6), 2 to 6 % essential oil. AMI offers an extract titrated in pheneolic compounds.

Moisturizing cucumber

Cucumis sativus L.

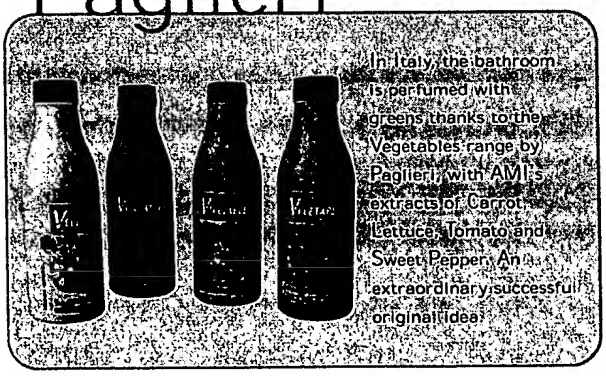
Cucumber has moisturizing and refreshing properties. It can be used in many cosmetic extracts, especially in face creams (dry and sensitive skin) and in after-sun products. The fresh pulp and the juice have soothing properties, they relieve skin and scalp irritations. Cucumber fruit contain osides (sucrose), protids among which amino acids (arginine) and enzymes (carboxylase, diastase), lipids, mineral matters (copper, iron, iodine, magnesium and zinc), organic acids (ascorbic acid), terpenoids (carotenoids), vitamins (thiamine, adenine). An extract titrated in proteins is available.

Tonic watercress

Nasturtium officinale R. Br

Watercress has astringent, purifying, remineralizing and tonic activities. Watercress extracts are particularly appreciated in hair care products (for greasy hair, delicate and damaged hair) and against hair loss. They are also appreciated in body and mouth products. Lastly, watercress is a first choice ingredient in face care products for combination, oily and mature skin. Watercress contains sulphurated derivatives, mineral matters (calcium, iron, iodine, manganese and potassium), organic acids among which ascorbic acid, vitamins (retinol, carotenoids, thiamine, riboflavine and calciferol). The extract offered by AMI is titrated in flavonoids.

Paglieri



In Italy, the bathroom is perfumed with greens thanks to the «Vegetables range by Paglieri» with AMI's extracts of Carrot, Lettuce, Tomato and Sweet Pepper. An extraordinary successful original idea!

CONTACT : info@albanmuller.com

Jardins de Beauté

Once upon a time was Jardins de Beaute or the Nice Story of Potimarron® : it highlights all the resources and the creativity of "Le Natural Product Designer", from the new plant extract laboratory development to the marketing and commercial back up via formulation consultancy.

Native to South America, it is at the Ferme de Sainte Marthe in Sologne - centre of France - (since then European Centre for Organical Farming) that this funny fruit-vegetable was introduced in France 20 years ago. Looking like a pumpkin but tasting like horse chestnut, its cultivar was called Potimarron®.

Appreciated for its gustative and nutritional qualities, Potimarron® disclosed other virtues : it made the skin of its harvesters smoother and smoother. Given these puzzling qualities, a real team was set up and Jardins de Beauté (Gabriel Dornay supported by AMI's infrastructure and expertise) was born. Analysis revealed that Potimarron® was crammed with provitamin A. Tests and developments followed one another in our laboratories during several years until an extract was obtained, prelude to a whole range of finished cosmetics. The marketing and commercial departments then took over: claims of the range, leaflets, packaging.

Launched in the «selective spaces» of the Carrefour hypermarkets, Jardins de Beauté marketed (in exclusivity) a whole range of products based on this new incomparable biological base. First in Europe, this range boasted with the special mention «based on organic plants». AMI further offered a true high-rank bosky bower to this precious active principle thanks to its first press vegetable oils and natural emulsifiers.

After the stunning feeling of freshness and the euphoria of renewal, have a go with the elegant generosity of greediness, be sure of your skin with healthy products.

[Code of Federal Regulations]
[Title 21, Volume 3]
[Revised as of April 1, 2001]
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[CITE: 21CFR173.240]

[Page 126-127]

TITLE 21--FOOD AND DRUGS

CHAPTER I--FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES (CONTINUED)

PART 173--SECONDARY DIRECT FOOD ADDITIVES PERMITTED IN FOOD FOR HUMAN CONSUMPTION--

Subpart C--Solvents, Lubricants, Release Agents and Related Substances

Sec. 173.240 Isopropyl alcohol.

Isopropyl alcohol may be present in the following foods under the conditions specified:

(a) In spice oleoresins as a residue from the extraction of spice, at a level not to exceed 50 parts per million.

(b) In lemon oil as a residue in production of the oil, at a level not to exceed 6 parts per million.

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(c) In hops **extract** as a residue from the extraction of hops at a level not to exceed 2.0 percent by weight: Provided, That,

(1) The hops **extract** is added to the wort before or during cooking in the manufacture of beer.

(2) The label of the hops **extract** specifies the presence of the isopropyl alcohol and provides for the use of the hops **extract** only as prescribed by paragraph (c)(1) of this section.

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CHAPTER I--FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES (CONTINUED)

PART 184--DIRECT FOOD SUBSTANCES AFFIRMED AS GENERALLY RECOGNIZED AS SAFE--Table of

Subpart B--Listing of Specific Substances Affirmed as GRAS

Sec. 184.1262 Corn silk and corn silk extract.

(a) Corn silk is the fresh styles and stigmas of Zea mays L. collected when the corn is in milk. The filaments are extracted with dilute ethanol to produce corn silk extract. The extract may be concentrated at a temperature not exceeding 60 deg.C.

(b) The Food and Drug Administration, in cooperation with the National Academy of Sciences, is developing food-grade specifications for corn silk and corn silk extract. In the interim, this ingredient must be of a suitable purity for its intended use.

(c) In accordance with Sec. 184.1(b)(2), the ingredients are used in food only within the following specific limitations:

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Category of food	Maximum level of use in food (as served)\1\	Functional use
Baked goods and baking mixes, Sec. 170.3(n)(1) of this chapter.	30	Flavoring agent, Sec. 170.3(o)(12) of this chapter.
Nonalcoholic beverages, Sec. 170.3(n)(3) of this chapter.	20	Do.
Frozen dairy desserts, Sec. 170.3(n)(20) of this chapter.	10	Do.
Soft candy, Sec. 170.3(n)(38) of this chapter.	20	Do.
All other food categories.....	4	Do.

\1\ Parts per million.

(d) Prior sanctions for this ingredient different from the uses established in this section do not exist or have been waived.

[47 FR 29953, July 9, 1982]

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TITLE 21--FOOD AND DRUGS

CHAPTER I--FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES--(Continued)

PART 573--FOOD ADDITIVES PERMITTED IN FEED AND DRINKING WATER OF ANIMALS--Table of

Subpart B--Food Additive Listing

Sec. 573.520 Hemicellulose **extract**.

Hemicellulose **extract** may be safely used in animal feed when incorporated therein in accordance with the following conditions:

(a) The additive is produced from the aqueous **extract** obtained by the treatment of wood with water at elevated temperatures (325 degrees-535 degrees F) and pressure (80 to 900 pounds per square inch) and contains primarily pentose and hexose sugars.

(b) The additive may be used in a liquid or dry state with the liquid product containing not less than 55 percent carbohydrate and the dry product containing not less than 84 percent carbohydrate.

(c) The additive is used as a source of metabolizable energy in animal feed in accordance with good manufacturing and feeding practices.

[41 FR 38652, Sept. 10, 1976, as amended at 43 FR 11181, Mar. 17, 1978]

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PART 184--DIRECT FOOD SUBSTANCES AFFIRMED AS GENERALLY RECOGNIZED AS SAFE--Table of

Subpart B--Listing of Specific Substances Affirmed as GRAS

Sec. 184.1445 Malt syrup (malt **extract**).

(a) Malt is the product of barley (Hordeum vulgare L.) germinated under controlled conditions. Malt syrup and **malt extract** are interchangeable terms for a viscous concentrate of water **extract** of germinated barley grain, with or without added safe preservative. Malt syrup is usually a brown, sweet, and viscous liquid containing varying amounts of amylolytic enzymes and plant constituents. Barley is first softened after cleaning by steeping operations and then allowed to germinate under controlled conditions. The germinated grain then undergoes processing, such as drying, grinding, extracting, filtering, and evaporating, to produce malt syrup (malt **extract**) with 75 to 80 percent solids or dried malt syrup with higher solids content.

(b) FDA is developing food-grade specifications for malt syrup (malt **extract**) in cooperation with the National Academy of Sciences. In the interim, the ingredient must be of a purity suitable for its intended use.

(c) In accordance with Sec. 184.1(b)(1), the ingredient is used in food with no limitation other than current good manufacturing practice. The affirmation of this ingredient as generally recognized as safe (GRAS) as a direct human food ingredient is based upon the following current good manufacturing practice conditions of use:

(1) The ingredient is used as a flavoring agent and adjuvant as defined in Sec. 170.3(o)(12) of this chapter.

(2) The ingredient is used in food at levels not to exceed current good manufacturing practice.

(d) Prior sanctions for this ingredient different from the uses established in this section do not exist or have been waived.

[48 FR 51613, Nov. 10, 1983]

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CHAPTER I--FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES (CONTINUED)

PART 184--DIRECT FOOD SUBSTANCES AFFIRMED AS GENERALLY RECOGNIZED AS SAFE--Table of

Subpart B--Listing of Specific Substances Affirmed as GRAS

Sec. 184.1560 Ox bile extract.

(a) Ox bile extract (CAS Reg. No. 8008-63-7), also known as purified oxgall or sodium choleate, is a yellowish green, soft solid, with a partly sweet, partly bitter, disagreeable taste. It is the purified portion of the bile of an ox obtained by evaporating the alcohol extract of concentrated bile.

(b) Food-grade ox bile extract shall meet the specifications of the U.S. Pharmacopeia (USP), XIV, 1950, p. 410.\1\

\1\ Copies may be obtained from: U.S. Pharmacopeial Convention, Inc., 12601 Twinbrook Parkway, Rockville, MD 20852.

(c) The ingredient is used as a surfactant as defined in Sec. 170.3(o)(29) of this chapter.

(d) The ingredient is used in food in accordance with Sec. 184.1(b)(1) at levels not to exceed good manufacturing practice. Current good manufacturing practice results in a maximum level, as served, of 0.002 percent for cheese as defined in Sec. 170.3(n)(5) of this chapter.

(e) Prior sanctions for this ingredient different from the uses established in this section do not exist or have been waived.

[43 FR 36064, Aug. 15, 1978. Redesignated and amended at 50 FR 49537, Dec. 3, 1985]

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CHAPTER I--FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES (CONTINUED)

PART 172--FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTIO

Subpart F--Flavoring Agents and Related Substances

Sec. 172.580 Safrole-free **extract** of sassafras.

The food additive safrole-free **extract** of sassafras may be safely used in accordance with the following prescribed conditions:

(a) The additive is the aqueous **extract** obtained from the root bark of the plant Sassafras albidum (Nuttall) Nees (Fam. Lauraceae).

(b) It is obtained by extracting the bark with dilute alcohol, first concentrating the alcoholic solution by vacuum distillation, then diluting the concentrate with water and discarding the oily fraction.

(c) The purified aqueous **extract** is safrole-free.

(d) It is used as a flavoring in food.

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TITLE 21--FOOD AND DRUGS

CHAPTER I--FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES

PART 73--LISTING OF COLOR ADDITIVES EXEMPT FROM CERTIFICATION--Table of Contents

Subpart A--Foods

Sec. 73.170 Grape skin **extract** (enocianina).

(a) Identity. (1) The color additive grape skin extract (enocianina) is a purplish-red liquid prepared by the aqueous extraction (steeping) of the fresh deseeded marc remaining after grapes have been pressed to produce grape juice or wine. It contains the common components of grape juice; namely, anthocyanins, tartaric acid, tannins, sugars, minerals, etc., but not in the same proportions as found in grape juice. During the steeping process, sulphur dioxide is added and most of the extracted sugars are fermented to alcohol. The **extract** is concentrated by vacuum evaporation, during which practically all of the alcohol is removed. A small amount of sulphur dioxide may be present.

(2) Color additive mixtures for food use made with grape skin **extract** (enocianina) may contain only those diluents listed in this subpart as safe and suitable in color additive mixtures for coloring foods.

(b) Specifications. Grape skin **extract** (enocianina) shall conform to the following specifications:

Pesticide residues, not more than permitted in or on grapes by regulations promulgated under section 408 of the Federal Food, Drug, and Cosmetic Act.
Lead (as Pb), not more than 10 parts per million.
Arsenic (as As), not more than 1 part per million.

(c) Uses and restrictions. Grape skin **extract** (enocianina) may be safely used for the coloring of still and carbonated drinks and ades, beverage bases, and alcoholic beverages subject to the following restrictions:

(1) It may not be used to color foods for which standards of identity have been promulgated under section 401 of the act unless artificial color is authorized by such standards.

(2) Its use in alcoholic beverages shall be in accordance with the provisions of parts 4 and 5, title 27 CFR.

(d) Labeling requirements. The label of the color additive and any mixtures prepared therefrom intended solely or in part for coloring purposes shall conform to the requirements of Sec. 70.25 of this chapter. The common or usual name of the color additive is ``grape skin **extract**'' followed, if desired, by ``(enocianina)''.

(e) Exemption from certification. Certification of this color additive is not necessary for the protection of the public health, and therefore batches thereof are exempt from the certification requirements of section 721(c) of the act.

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CHAPTER I--FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES

PART 73--LISTING OF COLOR ADDITIVES EXEMPT FROM CERTIFICATION--Table of Contents

Subpart A--Foods

Sec. 73.30 Annatto **extract**.

(a) Identity. (1) The color additive annatto extract is an extract prepared from annatto seed, Bixa orellana L., using any one or an appropriate combination of the food-grade extractants listed in paragraph (a)(1) (i) and (ii) of this section:

(i) Alkaline aqueous solution, alkaline propylene glycol, ethyl alcohol or alkaline solutions thereof, edible vegetable oils or fats, mono- and diglycerides from the glycerolysis of edible vegetable oils or fats. The alkaline alcohol or aqueous extracts may be treated with food-grade acids to precipitate annatto pigments, which are separated from the liquid and dried, with or without intermediate recrystallization, using the solvents listed under paragraph (a)(1)(ii) of this section. Food-grade alkalis or carbonates may be added to adjust alkalinity.

(ii) Acetone, ethylene dichloride, hexane, isopropyl alcohol, methyl alcohol, methylene chloride, trichloroethylene.

(2) Color additive mixtures for food use made with annatto **extract** may contain only diluents that are suitable and that are listed in this subpart as safe in color additive mixtures for coloring foods.

(b) Specifications. Annatto **extract**, including pigments precipitated therefrom, shall conform to the following specifications:

(1) Arsenic (as As), not more than 3 parts per million; lead as Pb, not more than 10 parts per million.

(2) When solvents listed under paragraph (a)(1)(ii) of this section are used, annatto **extract** shall contain no more solvent residue than is permitted of the corresponding solvents in spice oleoresins under applicable food additive regulations in parts 170 through 189 of this chapter.

(c) Uses and restrictions. Annatto **extract** may be safely used for coloring foods generally, in amounts consistent with good manufacturing practice, except that it may not be used to color foods for which standards of identity have been promulgated under section 401 of the act unless added color is authorized by such standards.

(d) Labeling. The label of the color additive and any mixtures prepared therefrom and intended solely or in part for coloring purposes shall conform to the requirements of Sec. 70.25 of this chapter. Labels shall bear information showing that the color is derived from annatto seed. The requirements of Sec. 70.25(a) of this chapter that all ingredients shall be listed by name shall not be construed as requiring the declaration of residues of solvents listed in paragraph (a)(1)(ii) of this section.

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(e) Exemption from certification. Certification of this color additive is not necessary for the protection of the public health and

therefore batches thereof are exempt from the certification requirements of section 721(c) of the act.

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CHAPTER I--FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES

PART 73--LISTING OF COLOR ADDITIVES EXEMPT FROM CERTIFICATION--Table of Contents

Subpart A--Foods

Sec. 73.100 Cochineal **extract**; carmine.

(a) Identity. (1) The color additive cochineal **extract** is the concentrated solution obtained after removing the alcohol from an aqueous-alcoholic **extract** of cochineal (Dactylopius coccus costa (Coccus cacti L.)). The coloring principle is chiefly carminic acid.

(2) The color additive carmine is the aluminum or calcium-aluminum lake on an aluminum hydroxide substrate of the coloring principles, chiefly carminic acid, obtained by an aqueous extraction of cochineal (Dactylopius coccus costa (Coccus cacti L.)).

(3) Color additive mixtures for food use made with cochineal **extract** or carmine may contain only diluents that are suitable and that are listed in this

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subpart as safe in color additive mixtures for coloring foods.

(b) Specifications. (1) Cochineal **extract** shall conform to the following specifications:

pH, not less than 5.0 and not more than 5.5 at 25 deg.C.
Protein (N x 6.25), not more than 2.2 percent.
Total solids, not less than 5.7 and not more than 6.3 percent.
Methyl alcohol, not more than 150 parts per million.
Lead (as Pb), not more than 10 parts per million.
Arsenic (as As), not more than 1 part per million.
Carminic acid, not less than 1.8 percent.

(2) Carmine shall conform to the following specifications:

Volatile matter (at 135 deg.C. for 3 hours), not more than 20.0 percent.
Ash, not more than 12.0 percent.
Lead (as Pb), not more than 10 parts per million.
Arsenic (as As), not more than 1 part per million.
Carminic acid, not less than 50.0 percent.

Carmine and cochineal **extract** shall be pasteurized or otherwise treated to destroy all viable Salmonella microorganisms. Pasteurization or such other treatment is deemed to permit the adding of safe and suitable substances (other than chemical preservatives) that are essential to the method of pasteurization or other treatment used. For the purposes of this paragraph, safe and suitable substances are those substances that perform a useful function in the pasteurization or other treatment to render the carmine and cochineal **extract** free of viable Salmonella

microorganisms, which substances are not food additives as defined in section 201(s) of the act or, if they are food additives as so defined, are used in conformity with regulations established pursuant to section 409 of the act.

(c) Uses and restrictions. Carmine and cochineal **extract** may be safely used for coloring foods generally in amounts consistent with good manufacturing practice, except that they may not be used to color foods for which standards of identity have been promulgated under section 401 of the act unless added color is authorized by such standards.

(d) Labeling requirements. The label of the color additives and any mixtures intended solely or in part for coloring purposes prepared therefrom shall conform to the requirements of Sec. 70.25 of this chapter.

(e) Exemption from certification. Certification of these color additives is not necessary for the protection of the public health, and therefore batches thereof are exempt from the certification requirements of section 721(c) of the act.

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TITLE 21--FOOD AND DRUGS

CHAPTER I--FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES--CONTINUED

PART 169--FOOD DRESSINGS AND FLAVORINGS--Table of Contents

Subpart B--Requirements for Specific Standardized Food Dressings and Flavorings

Sec. 169.175 Vanilla extract.

(a) Vanilla extract is the solution in aqueous ethyl alcohol of the sapid and odorous principles extractable from vanilla beans. In vanilla extract the content of ethyl alcohol is not less than 35 percent by volume and the content of vanilla constituent, as defined in Sec. 169.3(c), is not less than one unit per gallon. The vanilla constituent may be extracted directly from vanilla beans or it may be added in the form of concentrated vanilla extract or concentrated vanilla flavoring or vanilla flavoring concentrated to the semisolid form called vanilla oleo-resin. Vanilla extract may contain one or more of the following optional ingredients:

(1) Glycerin.
(2) Propylene glycol.
(3) Sugar (including invert sugar).
(4) Dextrose.
(5) Corn sirup (including dried corn sirup).

(b)(1) The specified name of the food is ``Vanilla extract'' or ``Extract of vanilla''.

(2) When the vanilla extract is made in whole or in part by dilution of vanilla oleoresin, concentrated vanilla extract, or concentrated vanilla flavoring, the label shall bear the statement ``Made from _____'' or ``Made in part from _____'', the blank being filled in with the name or names ``vanilla oleoresin'', ``concentrated vanilla extract'', or ``concentrated vanilla flavoring'', as appropriate. If the article contains two or more units of vanilla constituent, the name of the food shall include the designation ``__-fold'', the blank being filled in with the whole

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number (disregarding fractions) expressing the number of units of vanilla constituent per gallon of the article.

(3) Wherever the name of the food appears on the label so conspicuously as to be easily seen under customary conditions of purchase, the labeling required by paragraph (b)(2) of this section shall immediately and conspicuously precede or follow such name, without intervening written, printed, or graphic matter.

(c) Label declaration. Each of the ingredients used in the food shall be declared on the label as required by the applicable sections of parts 101 and 130 of this chapter.

[42 FR 14479, Mar. 15, 1977, as amended at 58 FR 2886, Jan. 6, 1993]

ExtractsPlus Recommends Guidelines for FDA Regulations in the Nutritional Supplement Industry

JAN. 21. 12:55AM

PRESS RELEASE

For Release, Immediately
Date: January 15,1998

For more information, call Staci Eisner, Technical Director
or Bill Roberts, President

Carlsbad, CA.-- The FDA's recent labeling rule has sparked heated discussion in the health supplement industry. This reaction led the FDA to invite industry input. ExtractsPlus, a distributor of botanical extracts, responded with specific recommendations. The main provisions of ExtractsPlus' petition can be summarized as follows:

1. Establish definitions for botanical extracts.

In order to implement rules for the labeling of botanical extracts, it is essential first to define what constitutes such an extract. There are a great variety of materials represented, with a greater or lesser degree of accuracy, as plant extracts. For example, there may be confusion between the pressed, dried juice of a plant and the extracts of the plant. Furthermore, the term "native extract" is often misunderstood. ExtractsPlus has proposed specific definitions for terms related to botanical extracts.

2. Establish a methodology to distinguish different types of extracts, without requiring confusing statements about the solvents used.

The FDA's latest ruling requires product labels to disclose the solvents used to make an extract, even when the solvents are removed to dryness. Extracts made from the same herb but using different solvents can have very different biochemical properties. For example, the beneficial fatty acids found in saw palmetto can only be extracted using special solvents which are chemically compatible with the fatty acids. For this reason, it is important for consumers to know how the extracts they buy were made Then if they are dissatisfied with the results obtained with one type of extract, they could switch to a different type.

Some members of the nutritional supplement industry are concerned that the practice of listing solvents may lead consumers to erroneously believe that significant solvent residues remain in the products. To avoid this confusion ExtractsPlus is proposing a system of solvent categorization. For example water-based extracts would be in one category, ethanol-based extracts in another, and so on. Product labels would list the category of solvent. The explicit naming of the solvent would be

unnecessary.

ExtractsPlus believes this scheme would help educate consumers to differentiate between products nominally containing the same herb. It would also assist marketers in creating brand distinction, and dosage form manufacturers in buying consistent raw materials.

3. The terms "extracts" and "raw herbs" should not be used interchangeably

Some manufacturers of health supplements use extracts as the "source" of an herb. For example, they might use 1 mg of a 50:1 extract and then label the product as containing 50 mg of herb. This sourcing is misleading to the consumer, and shows the great variance in potency of herbal supplements that may currently have the same information on their labels. An extract by definition cannot contain all the components of the raw herb. Therefore an extract should never be considered or used as the source of a plant for manufacturing purposes.

4. Plant:extract ratio notation should be clarified and disclosed.

The FDA's latest ruling defines a plant:extract ratio for use on the rebels of liquid extracts, but ignores any similar provision for powdered extracts. ExtractsPlus believes that this is a serious omission. Currently, there are several alternative ways to notate the plant:extract ratio. Let's say 4 kilos of herb are processed into 1 kilo of extract. The resulting powder could be described as a 4:1, a 1:4 or a 4x extract. When fillers are included in the computation of ratios, the issue is further complicated. The ratio confusion is exacerbated as it extends from the raw materials to the end product purchased by the buying public. ExtractsPlus recommends that the FDA establish standards for ratio notation used in labeling powdered extracts.

5. Amount of filler in powdered extracts should be taken into account

Even when plant:extract ratios are the same, the amount of filler used in powdered extracts can vary considerably. For example, a crude plant extract containing no filler would typically have a ratio of 5:1 and would contain a broad spectrum of the components naturally occurring in the plant. However, a 5:1 extract could also be manufactured by diluting a highly concentrated 100:1 extract with 95% filler. This latter extract would contain only a few of the plant's native principles. ExtractsPlus believes that it is important for consumers, formulators, and supplement manufacturers alike to discern the amount of filler. This can be handled either by excluding the amount of filler in the calculation of extract ratios, or explicitly stating the filler volume on product labels.

6. Supplement manufacturers, above all, need access to vital information.

Due to the complexity of the botanical extract market, it is difficult to formulate labeling guidelines which will accurately and universally convey each product's important qualities to the consumer. However, in order to ensure consistent quality, ExtractsPlus recommends that supplement manufacturers, at least, have access to all of this information, including:

- extraction solvent (type and concentration)

- plant:extract ratio, including ranges if applicable

- complete ingredient disclosure (including the type and concentration or range of concentration of any

and all excipients.)

This will enable dosage form manufacturers to accurately compare raw materials from different vendors and will thereby facilitate batch-to-batch consistency in products reaching the consumer.

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